

IN THE CLAIMS:

Please amend claims 169, 171, 172 and 174, cancel claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147, 148, 150-168, 170, and 173, and new claims 175-198.

This listing of claims will replace all prior versions, and listings of the claims in the application.

Listing of the claims

1-168. (Canceled)

169. **(Currently amended)** A method of treating an individual who has killing primary or metastasized colorectal, cancer or primary or metastasized gastric or esophageal cancer cells in an individual who has been identified as having primary or metastasized colorectal, cancer or primary or metastasized gastric or esophageal cancer, said method comprising the steps in the following order:

a) administering to said individual a cytostatically effective amount of an unconjugated guanylyl cyclase C ligand sufficient to inhibit cell proliferation by the cytostatic effect of the guanylyl cyclase C ligand for at least 6 hours wherein, wherein said guanylyl cycles C ligand activates guanylyl cyclase C on cancer cells, wherein guanylyl cyclase C ligand molecules bind to guanylyl cyclase C on the surface of a primary or metastasized colorectal, gastric or esophageal cancer cell in said individual and inhibit proliferation of said cells and wherein the cytostatically effective amount of a guanylyl cyclase C ligand is an amount sufficient to maintain a plasma concentration $\geq EC_{50}$ of said guanylyl cyclase C ligand and

b) subsequently after administration of said guanylyl cycles C ligand is completed administering a therapeutically effective amount of a different cytotoxic therapeutic agent or radiation.

170. (Canceled)

171. **(Currently amended)** The method of claim 169 or 170, wherein said ~~different~~ cytotoxic therapeutic agent is selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabinoside, etoposide, 5- fluorouracil, melphalan, chlorambucil, cisplatin, vindesine, mitomycin, bleomycin, purothionin, macromomycin, 1,4 benzoquinone derivatives, trenimon, ricin, ricin A chain, Pseudomonas exotoxin, diphtheria toxin, Clostridium perfringens phospholipase C, bovine pancreatic ribonuclease, pokeweed antiviral protein, abrin, abrin A chain, cobra venom factor, gelonin, saporin, modeccin, viscumin, volkensin, nitroimidazole, metronidazole and misonidazole.

172. **(Currently amended)** The method of claim 169 or 170, wherein the individual has been identified as having metastatic colorectal, esophageal or stomach cancer.

173. **(Canceled)**

174. **(Currently amended)** The method of claims 64, 65, or claim 169, wherein the cytostatically effective amount of a guanylyl cyclase C ligand is an amount sufficient to maintain a concentration of greater than or equal to 10 times the EC₅₀ of said guanylyl cyclase C ligand.

175. **(New)** The method of claim 169 wherein said cytotoxic therapeutic agent is a guanylyl cyclase C ligand conjugated to a cytotoxic moiety.

176. **(New)** The method of claim 175 wherein said cytotoxic therapeutic agent is an anti-guanylyl cyclase C antibody conjugated to a cytotoxic moiety.

177. **(New)** The method of claim 169 wherein the guanylyl cyclase C ligand that activates guanylyl cyclase C on cancer cells is administered in an amount sufficient to inhibit cell proliferation by the cytostatic effect of the guanylyl cyclase C ligand for at least 8 hours.

178. (New) The method of claim 169 wherein the guanylyl cyclase C ligand that activates guanylyl cyclase C on cancer cells is administered in an amount sufficient to inhibit cell proliferation by the cytostatic effect of the guanylyl cyclase C ligand for at least 12 hours.

179. (New) The method of claim 169 wherein the guanylyl cyclase C ligand that activates guanylyl cyclase C on cancer cells is administered in an amount sufficient to inhibit cell proliferation by the cytostatic effect of the guanylyl cyclase C ligand for at least 16 hours.

180. (New) The method of claim 169 wherein the guanylyl cyclase C ligand that activates guanylyl cyclase C on cancer cells is administered in an amount sufficient to inhibit cell proliferation by the cytostatic effect of the guanylyl cyclase C ligand for at least 20 hours.

181. (New) The method of claim 169 wherein the guanylyl cyclase C ligand that activates guanylyl cyclase C on cancer cells is administered in an amount sufficient to inhibit cell proliferation by the cytostatic effect of the guanylyl cyclase C ligand for at least 24 hours.

182. (New) The method of claim 169 wherein said guanylyl cyclase C ligand that activates guanylyl cyclase C on cancer cells is administered intravenously.

183. (New) The method of claim 169 wherein said guanylyl cyclase C ligand that activates guanylyl cyclase C is administered for 7-15 days followed by treatment using said cytotoxic agent.

184. (New) The method of claim 169 wherein said guanylyl cyclase C ligand that activates guanylyl cyclase C is administered for 30 days followed by treatment using said cytotoxic agent.

185. (New) The method of claim 169 comprising administering more than one cytotoxic agent

186. (**New**) The method of claim 169 comprising administering one cytotoxic agent that selectively kills cells in S phase and one cytotoxic drug that selectively kills cells in G1 phase.

187. (**New**) The method of claim 169 wherein said cytotoxic therapeutic agent is selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabinoside, etoposide, 5- fluorouracil, melphalan, chlorambucil, cis-platin, vindesine, mitomycin, bleomycin, purothionin, macromomycin, 1,4 benzoquinone derivatives, , nitroimidazole, metronidazole and misonidazole.

188. (**New**) A method of treating an individual who has metastasized colorectal, cancer or primary or metastasized gastric or esophageal cancer in an individual who has been identified as having metastasized colorectal, cancer or primary or metastasized gastric or esophageal cancer, said method comprising the steps in the following order:

- a) administering to said individual an amount of an guanylyl cyclase C ligand that activates guanylyl cyclase C on cancer cells effective to increase the number of guanylyl cyclase C molecules on the surface of cancer cells, and
- b) subsequently administering a therapeutically effective amount of a guanylyl cyclase C ligand that is conjugated to a cytotoxic moiety.

189. (**New**) The method of claim 188 wherein the individual has been identified as having metastatic colorectal, esophageal or stomach cancer.

190. (**New**) The method of claim 188 wherein said guanylyl cyclase C ligand that is conjugated to a cytotoxic moiety is an anti-guanylyl cyclase C antibody conjugated to a cytotoxic moiety or an anti-guanylyl cyclase C binding fragment of an anti-guanylyl cyclase C antibody conjugated to a cytotoxic moiety.

191. (New) The method of claim 188 wherein said guanylyl cyclase C ligand that is conjugated to a cytotoxic moiety is an anti-guanylyl cyclase C antibody conjugated to a cytotoxic moiety.
192. (New) The method of claim 188 wherein the guanylyl cyclase C ligand that activates guanylyl cyclase C on cancer cells is administered in an amount effective to increase the number of guanylyl cyclase C molecules on the surface of cancer cells for at least 6 hours.
193. (New) The method of claim 188 wherein the guanylyl cyclase C ligand that activates guanylyl cyclase C on cancer cells is administered in an amount effective to increase the number of guanylyl cyclase C molecules on the surface of cancer cells for at least 8 hours.
194. (New) The method of claim 188 wherein the guanylyl cyclase C ligand that activates guanylyl cyclase C on cancer cells is administered in an amount effective to increase the number of guanylyl cyclase C molecules on the surface of cancer cells for at least 12 hours.
195. (New) The method of claim 188 wherein the guanylyl cyclase C ligand that activates guanylyl cyclase C on cancer cells is administered in an amount effective to increase the number of guanylyl cyclase C molecules on the surface of cancer cells for at least 16 hours.
196. (New) The method of claim 188 wherein the guanylyl cyclase C ligand that activates guanylyl cyclase C on cancer cells is administered in an amount effective to increase the number of guanylyl cyclase C molecules on the surface of cancer cells for at least 20 hours.
197. (New) The method of claim 188 wherein the guanylyl cyclase C ligand that activates guanylyl cyclase C on cancer cells is administered in an amount effective to increase the number of guanylyl cyclase C molecules on the surface of cancer cells for at least 24 hours.

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198. (**New**) The method of claim 188 wherein said guanylyl cyclase C ligand that activates guanylyl cyclase C on cancer cells is administered intravenously.